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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,327	09/02/2004	Shingo Hiramatsu	0210-0190PUS1	1247
2292 7590 04/18/2007 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			EXAMINER PRIEBE, SCOTT DAVID	
			ART UNIT	PAPER NUMBER
			1633	
SHORTENED STATUTORY PERIOD OF RESPONSE		NOTIFICATION DATE	DELIVERY MODE	
3 MONTHS		04/18/2007	ELECTRONIC	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary

Application No.

10/506,327

Applicant(s)

HIRAMATSU ET AL.

Examiner

Scott D. Priebe, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-41 is/are pending in the application.
- 4a) Of the above claim(s) 1-20, 40 and 41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-30, 32 and 39 is/are rejected.
- 7) ☒ Claim(s) 31 and 33-38 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

This application contains claims 1-20, 40, and 41 drawn to an invention nonelected with traverse in the paper filed 9/11/06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-20, 40, and 41 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Information Disclosure Statement

Applicant is incorrect that some of the cited references were not considered. All were considered, and no new copies of these references need be provided. The previous Office action simply indicates the limited extent to which documents BA and BB of the 8/31/05 IDS, BA of the 10/21/05 IDS, and CB of the 9/2/04 IDS could be considered; and that the citations on the PTO-1449 forms of documents CA-CD of the 8/31/05 IDS and CB of the 9/2/04 IDS were incomplete, and therefore inappropriate for printing on the face of a patent.

Should Applicant wish documents CA-CD of the 8/31/05 IDS and CB of the 9/2/04 IDS to be cited on the face of a patent, Applicant need only provide a supplemental PTO-1449 (not an

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entire IDS) that provides citations for each that comply with 37 CFR 1.98(b)(5). Since this action is final, the supplemental PTO-1449 should list only the above documents to avoid conflict with the provisions of 37 CFR 1.97(d). If Applicant is made aware of any newly discovered documents, they should be provided in a separate supplemental IDS that complies with 37 CFR 1.97(d).

Claim Objections

Claims 31 and 33-38 remain objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim may not depend from another multiple dependent claims, and also must depend from multiple claims in the alternative only. See MPEP § 608.01(n). In claim 31, "according to claims 22 and 23" is not in the alternative; replacing "and" with --or-- would be remedial. In addition, claims 34-37 are multiple dependent claims that depend from multiple dependent claims. Accordingly, the claims 31 and 33-38 have not been further treated on the merits.

Claims 21-24 are objected to because of the following informalities:

In claims 21-23, "a promoter active in *Bombyx mori* expressed in silk glands" is grammatically improper, and potentially confusing. It is suggest that this limitation in each of claims 21-23 be rewritten as -- a promoter expressed in *Bombyx mori* silk glands--.

In claim 24, "piggyBack" is misspelled, and should be --piggyBac--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim 28 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 remains indefinite for recitation of “the 3’ terminal portion ... is the DNA”. Claims 22 and 23, from which claim 28 depends, recite that the “cassette” comprises the promoter, 5’ terminal portion, and/or 3’ terminal portion. The juxtaposition of open language, i.e. “comprising” in the base claims and the closed language, “is” in claim 28 renders the scope of claims 28 ambiguous. It is unclear whether the claim excludes additional sequences from the 3’ terminal portion not found in the recited SEQ ID NO. For example, it is unclear whether a cassette comprising SEQ ID NO: 24 and additional sequences adjacent to SEQ ID NOs: 24 in the *B. mori* fibroin H-chain gene is embraced by claim 28 or not.

Claims 21, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites “inverted repetitive sequences of a pair of piggyBac transposons present on both sides of the gene cassette”. As written, it is unclear how many inverted repetitive sequences are on each side of the cassette. This appears to be the result of an imperfect translation of the original specification in Japanese. The drawings show a single copy of the piggyBac inverted repetitive sequences on each side of the cassette, and page 21, lines 2-4, describes a similar arrangement. If taken as a whole, the specification appears to teach that an

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inverted repetitive sequence of a piggyBac transposon is present on each side of the sequence comprising the promoter and gene. It is also unclear what actually is being claimed here. The preamble of claim 21 is directed to a gene cassette, while part (3) refers to the gene cassette as being part of something else. The cassette cannot contain the inverted repetitive sequences at the same time it is contained between the inverted repetitive sequences. It is suggested that claim 21 be amended by indicating the cassette comprises in order:

-
- (1) an inverted repetitive sequence of a piggyBac transposon;
 - (2) a promoter expressed in *Bombyx mori* silk glands;
 - (3) a gene coupled downstream from the promoter in which wherein the 5' terminal portion of a fibroin H chain gene of *Bombyx mori* is fused to the 5' side of an exogenous protein structural gene; and
 - (4) an inverted repetitive sequence of a piggyBac transposon.
-

Claim 25 recites the limitations "the portion" and "the first exon and second exon ..." in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102 & 103

Claims 22, 23, 25 and 27 remain rejected and claims 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (Acta Biochimica et Biophysica Sinica 33(1): 112-116, Jan. 2001) as evidenced by Zhang et al. (Acta Biochimica et Biophysica Sinica 31(2): 119-123, 1999) and GenBank Acc. No. AF226688 for the reasons of record set forth in the Office action of 10/30/06.

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With respect to claim 25, it is unclear (see rejection under 35 USC 112, second para., above) whether this claim simply requires the presence of a portion of the first and second exons, or whether they must be joined in the construct, i.e. the first intron is absent, or requires something else entirely. It has been included in the rejection on the assumption that it simply requires the presence of the portion.

Claims 26 and 28 are rejected under 35 U.S.C. 102(b) as anticipated by, as applied to claims 22, 23, 25 and 27 above; or, in the alternative, under 35 U.S.C. 103(a) as obvious over Zhao et al. (Acta Biochimica et Biophysica Sinica 33(1): 112-116, Jan. 2001) as evidenced by Zhang et al. (Acta Biochimica et Biophysica Sinica 31(2): 119-123, 1999) and GenBank Acc. No. AF226688, as applied to claims 21-25 and 28 above, and further in view of Zhou et al., Nucleic Acids Res. 28(12): 2413-2419, which cites and is cumulative over GenBank Acc. No. AF226688 for the reasons of record set forth in the Office action of 10/30/06.

With respect to claim 28, it is still ambiguous as to whether the 3' portion of the fibroin gene can comprise sequence adjacent to SEQ ID NO: 24 in the *B. mori* genome.

Applicant's arguments filed 3/30/07 have been fully considered but they are not persuasive. Applicant argues that the amendment of claims 21-23 incorporating the limitation of claim 31 overcomes the rejection. In response, only claim 21 (and thereby claim 24) was amended to incorporate this limitation.

Claims 21-23, 25, 27, 29, 30, 32, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al., US 2002/0137211 in view of Zhao et al. (Acta Biochimica et Biophysica Sinica 33(1): 112-116, Jan. 2001); Zhang et al. (Acta Biochimica et Biophysica Sinica 31(2): 119-123, 1999) and GenBank Acc. No. AF226688.

Liu et al. discloses a vector comprising a gene cassette encoding a fusion protein comprising spider dragline silk repetitive sequence inserted into the repetitive sequence of *B. mori* fibroin L-chain for making transgenic silkworms that then produce silk comprising the fusion protein as the L-chain. This vector and a second vector expressing piggyBac transposase are introduced into silkworm eggs to produce the transgenic silkworm. The gene cassette comprises in order: an inverted terminal repeat (ITR) of a piggyBac transposon; the promoter of the *B. mori* fibroin L-chain gene; the 5' part of a fibroin L-chain cDNA including 5' untranslated sequence and coding sequence of fibroin L-chain including the signal sequence; a foreign sequence encoding the repetitive amino acid region of spider dragline silk without a stop codon; the 3' part of the fibroin L-chain cDNA including the remainder of the L-chain coding sequence and 3' untranslated region; the transcription terminator sequence (polyA addition region) of the L-chain gene; and an ITR of a piggyBac transposon. The spider silk coding sequence is inserted into the coding sequence for the repetitive region of the L-chain. See entire document, especially Fig. 2, and ¶¶ 005-009, 0011-0012, 0014, 0039 and 0041. Liu does not suggest making the analogous construct using the fibroin H-chain gene sequences in place of the L-chain gene sequences.

However, Zhao discloses a transgenic silkworm with a genome comprising a gene cassette comprising, in order, the 5' end of the endogenous fibroin H-chain gene, including the

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promoter, exon 1, intron I, and the 5' end of exon II terminated by a PstI site, fused in-frame to a GFP coding sequence, fused in frame to coding sequence for a synthetic fibroin like sequence, fused in frame to a 3' terminal portion of the endogenous fibroin H-chain gene, comprising the three Cys residues, and the endogenous genomic sequence flanking the 3' end of the Fib-H coding sequence that include the transcription terminator. The GFP and fibroin-like coding sequences were inserted into the endogenous gene by gene targeting using the pUC53 vector of Zhang, such that the coding sequence for the repetitive regions of the Fib-H protein were replaced by the exogenous protein structural genes. See entire document, especially Section 2.2 and Fig. 1 (page 5), Fig. 2, and Fig. 5.

Zhang describes pUC53, and indicates that the 5' Fib-H targeting arm (5' flanking sequence) is the XhoI-PstI fragment that begins within intron I and extends into exon II (these sites correspond to the XhoI site at position 62922, and the PstI site at position 63854 of AF226688). The 3' end of instant SEQ ID NO: 22 and 23 corresponds to position 63153 of AF226688. The identity of the 3' targeting arm is less clear. However, Section 1.2.1 shows primers used to detect this sequence. The first primer (downstream of the MluI site, which is not present in the fib-H gene) is identical to the 17 nucleotide sequence beginning at position 78895 of AF226688, while the complement of the second primer is identical to the 17 nucleotides of AF226688 beginning at position 79141, which is the beginning of an EcoRI site. Section 2.2 and Fig. 2 indicate that this EcoRI site is over half-way downstream in the 3' targeting arm, which is 350 nucleotides in length, i.e. the 3' targeting arm extends over 175 nucleotides upstream of the EcoRI site. The MluI site in the first primer appears to correspond to the MluI site inserted into pUC19 in the construction of pUC53. Consequently, it appears that the 3' targeting arm begins at

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position 78895 of AF226688 and extends about 350 nucleotides downstream to about position 79245. Instant SEQ ID NO: 24 corresponds to positions 79099-79197, and so would correspond to the central region of the 3' targeting arm of pUC53.

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have made a gene cassette analagous to the one as described in Liu, but based on the *Bombyx mori* fibroin H-chain gene sequences corresponding to the the L-chain gene sequences used by Liu. Zhao demonstrated that silk comprising foreign repetitive sequences in the H-chain could be expressed in the silk of transgenic silkworms, just as Liu showed one could produce silk with the foreign repetitive sequences in the L-chain. Thus, one of skill in the art would recognize that the H-chain gene sequences and L-chain gene sequences were equivalents for producing transgenic silk.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

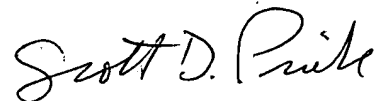
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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Scott D. Priebe, Ph.D.
Primary Examiner
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